

POTENTIAL DOSE ADJUSTMENT IMPLICATIONS RESULTING FROM CLONAZEPAM TABLET SPLITTING

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ABSTRACT

Tablet splitting is particularly interesting for dose tapering and slow dose titration, especially in psychiatric and geriatric communities. The objective of this study was to investigate the accuracy and precision of splitting clonazepam tablets using a kitchen knife and a commercially available tablet splitter. Whole tablets and split portions were individually weighed to determine weight variation and weight loss. Despite an accurate splitting (mean percentage close to 100%), precision analysis indicated a high variability in half-tablets weight (RSD>6%), ranging around $\pm 25\%$ for tablet splitter and $\pm 18\%$ for kitchen knife. There was no significant difference between the splitting techniques used to divide the tablets for both accuracy and weight loss. These preliminary findings indicate that splitting clonazepam tablets either by tablet splitter or kitchen knife might result in an apparent accurate splitting, in spite of the lack of precision between split portions. Future research is needed to investigate if such variations in clonazepam daily drug doses would result in clinical outcomes compromising dose adjustment schedules.

Descriptors: tablets, clonazepam, dosage.

Potenciais implicações no ajuste de doses decorrentes da divisão de comprimidos de clonazepam

RESUMO

A divisão de comprimidos permite o ajuste de dose e retirada gradual de medicamentos, principalmente para pacientes psiquiátricos e geriátricos. O objetivo deste estudo foi investigar a exatidão e precisão de doses das porções provenientes da divisão de comprimidos de clonazepam utilizando-se faca e cortador de comprimidos. Comprimidos inteiros e porções foram pesados individualmente para determinação da variação de peso e perda de peso. Apesar de uma divisão exata (próxima a 100%), a análise da precisão indicou alta variabilidade entre o peso das porções (DPR>6%), variando em torno de $\pm 25\%$ para o cortador de comprimidos e $\pm 18\%$ para a faca. Não houve diferença significativa entre as técnicas utilizadas quanto à exatidão e perda de peso. Esses dados preliminares indicam que dividir comprimidos de clonazepam tanto com o cortador de comprimidos quanto com a faca pode resultar em uma divisão aparentemente exata, apesar da falta de precisão entre as porções obtidas. Estudos são necessários para investigar se tais variações nas doses diárias de clonazepam resultariam em um desfecho clínico comprometendo esquemas de ajuste de doses.

Descritores: comprimidos, clonazepam, dosagem.

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Introdução

Tablet splitting is a common practice with the objective of allowing dose flexibility, easing swallowing for patients with difficult and reducing drug costs for both patients and healthcare providers.¹⁻³

Tablet splitting has been often used for both scored and non-scored tablets through different techniques, such as tablet splitter, kitchen knife, hand breaking and scissors.¹

One study found that more than 37% of all tablets used in an elderly care home in Canada were split and the most commonly split ones were psychotropic drugs (36.3%).⁴

Significant variation in drug content between the halves due to the uneven breaking of the tablet might compromise the treatment by under- or overdosing, which can be critical for psychoactive drugs, drugs with narrow therapeutic range and drugs with nonlinear pharmacokinetics.^{5,6}

Tablet splitting is particularly interesting for dose tapering and slow dose titration, especially in psychiatric and geriatric communities.⁷

Clonazepam dose adjustment takes into account factors like age, clinical response and tolerance to side effects of each individual patient. Recommended initial doses are 1.5mg/day or less in divided doses. Daily dose should be titrated until an effective dose is reached. Adult maintenance doses are usually between 4 to 8mg/day in divided doses as well.⁸ Abrupt discontinuation of treatment is associated with withdrawal symptoms,⁹ thus a gradual and careful tapering is needed when stopping taking the medication.¹⁰

In view of this, the present study was aimed at investigating the accuracy and precision of splitting clonazepam tablets by tablet splitter and kitchen knife through evaluation of weight uniformity.

Metodologia

Test samples consisted of 2mg clonazepam scored tablets from the same batch.

Tablet splitting

Tablet splitting was performed in a controlled laboratory environment using a kitchen knife and a commercially available tablet splitter. Two trained operators (1 and 2) performed all analyses to eliminate operator bias. The samples were named as follows: K1 (kitchen knife/ operator 1), K2 (kitchen knife/ operator 2), S1 (tablet splitter/ operator 1) and S2 (tablet splitter/ operator 2).

Weight measures

Twenty randomly selected tablets were weighed individually using the analytical balance, according to the "Weight determination" test contained in the Brazilian Pharmacopoeia,¹¹ before being split with a kitchen knife (K1 and K2) and a tablet splitter (S1 and S2). For each whole tablet the resulting split portions were randomly denominated as Split A and Split B. The split portions were individually weighed to determine weight variability.

Data analysis

Target weight of the split portions was fixed as equal to one-half of the whole tablet weight itself.

Accuracy was calculated as the percentage of split portions weight to target weight for each split portion.

Precision was calculated as the relative standard deviation expressed as a percentage (%RSD) for whole tablets and split portions. Whole tablets and split portions weight variation should present a %RSD <6% (proxy USP specification for %RSD) to be considered precise. The number of split portions falling outside the USP proxy recommended ranges of 85-115%, 75-125% and RSD<6% was reported.

Percentage of weight loss was calculated for each tablet. Weight loss of each tablet should be <3% when compared to the whole tablet weight.¹²

The weight of split portion A was compared to split portion B using a Student's t test for dependent samples, as well as the accuracy among groups. A Mann-Whitney U test and a Student's t test for independent samples were used to compare accuracy and percentage weight loss between the operators and splitting techniques. Statistical analyses were

performed on STATISTICA 12 (StatSoft, Tulsa, OK, USA). A p<0.05 was considered statistically significant.

RESULTADOS:

The current study was aimed at evaluating the effect of splitting tablets by kitchen knife or tablet splitter in order to obtain small clonazepam doses.

The accuracy and precision of split tablets are presented in Table 1. A more accurate split is indicated by the closeness to 100%. Tablets split with the tablet splitter and the kitchen knife by both operators presented a mean percentage close to 100%, indicating an accurate splitting; however, precision analysis indicated a high variability in half-tablets weight. Tablets split by kitchen knife showed more precision between split portions when compared to tablets split by tablet splitter; however, both techniques failed to meet the adopted criteria for precision.

Table 1. Accuracy, precision and weight loss of tablets split by tablet splitter and kitchen knife by two trained operators.

Splitting technique Operator	Split A n=20		Split B n=20		Weight loss (%a,d)	
	Accuracy (%a,b)	Precision (%RSD)c	Accuracy (%a,b)	Precision (%RSD)c		
S1	99.44 (75.43-124.78)	10.67	99.10 (64.79-121.46)	11.30	0.73	(0-5.22)
S2	97.73 (69.76-119.93)	12.78	100.04 (77.63-125.93)	12.01	1.12	(0-7.38)
K1	97.94 (70.67-115.84)	9.15	100.56 (84.04-119.74)	7.55	0.75	(0-4.80)
K2	99.73 (87.59-115.76)	6.89	98.45 (83.40-109.43)	6.03	0.91	(0-3.04)

S1= splitter/ operator 1

S2= splitter/ operator 2

K1= knife/ operator 1

K2= knife/ operator 2

a expressed as mean (minimum-maximum)

b calculated as the percentage of split portions weight to target weight for each split portion

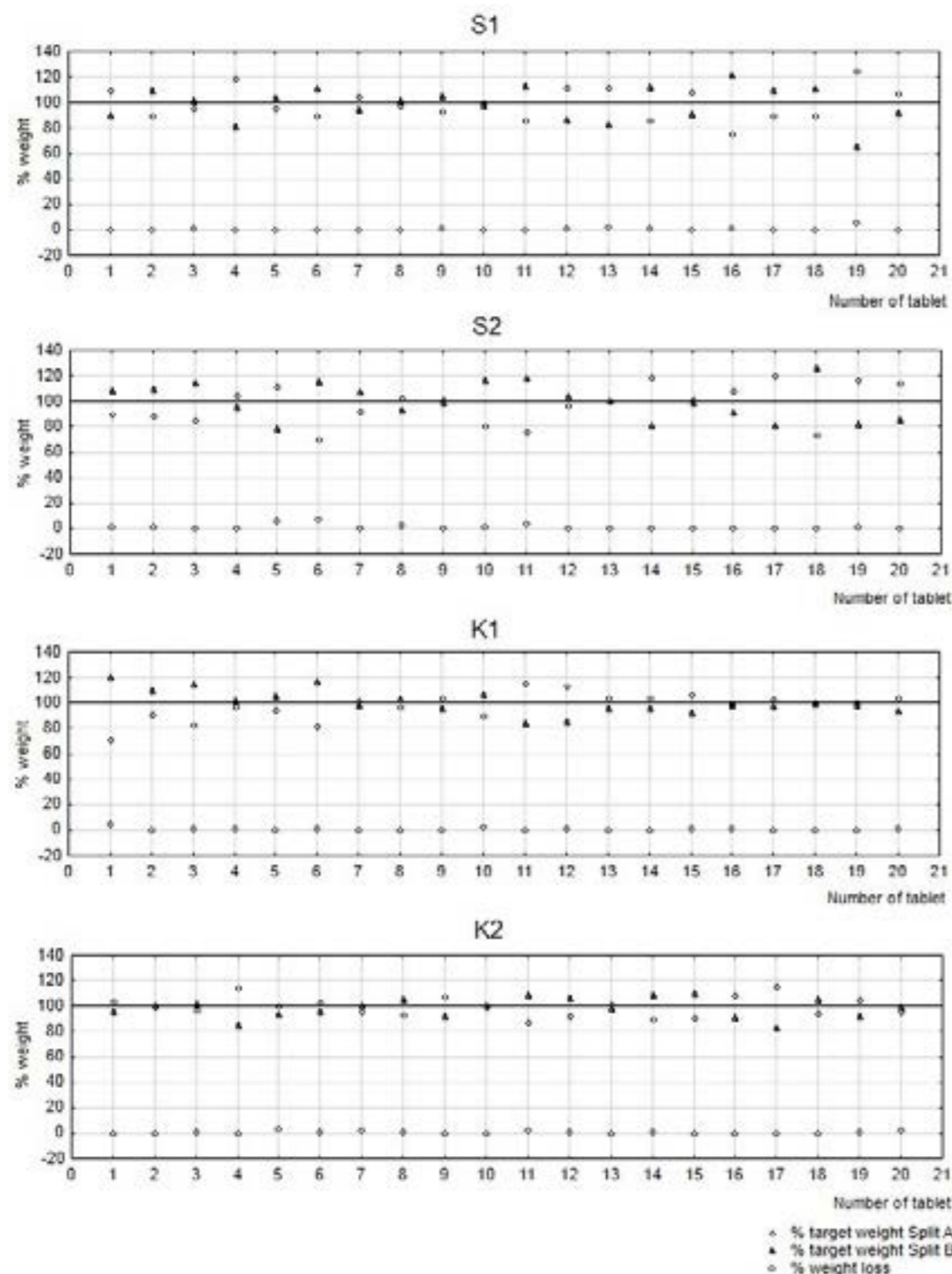
c calculated as the relative standard deviation expressed as a percentage

d calculated by subtracting the sum of the weights of the split portions from the whole tablet weight and expressed as a percentage

Weight loss in split tablets ranged from 0 to 7.38% when using the tablet splitter and from 0 to 4.80% when using the kitchen knife (Table 1).

There was no significant difference between the weight of corresponding split portions A and B. Accuracy among groups did not differ significantly. Further, no significant difference was observed between the splitting techniques and operators for accuracy and weight loss.

Accuracy and weight loss for each splitting technique performed by both operators is presented in Fig. 1, allowing visualization of individual deviation from target weight (100%).



operators using the kitchen knife and tablet splitter (S1= splitter/ operator 1; S2= splitter/ operator 2; K1= knife/ operator 1; K2= knife/ operator 2).

A total of 32 (20.0%) portions fell outside the range of 85-115%, while 5 (3.1%) fell outside the range of 75-125%. Split portions presented higher weight variation (RSD >6%) when compared to whole tablets (RSD= 2.5%). At least 1 tablet of each group presented a loss of mass > 3% after being split (Table 2).

Table 2. Number of split portions falling outside the ranges of 85-115% and 75-125%, presenting RSD > 6% and loss of mass > 3% for tablets split with tablet splitter and kitchen knife by two trained operators.

Splitting technique/ Operator	Number of portions outside the USP proxy range		RSD > 6% n=40	Tablets presenting loss of mass > 3% n=20
	85-115% n=40	75-125% n=40		
S1	n (%)	n (%)	Yes/No	n
S1	7 (17.5)	1 (2.5)	Yes	1
S2	16 (40)	3 (7.5)	Yes	3
K1	7 (17.5)	1 (2.5)	Yes	1
K2	2 (5)	0 (0)	Yes	1

S1= splitter/ operator 1
S2= splitter/ operator 2
K1= knife/ operator 1
K2= knife/ operator 2

In the present study, weight variation increased when comparing split tablets to intact ones, similarly to other studies.1,5,7,13-21 For instance, Tahaineh et al. (2012) found that 3 out of 4 drugs split with a kitchen knife failed to meet the adopted criteria for weight variation,19 as in the study performed by Elliott et al. (2014), in which 5 of 8 drugs were out of specification for expected weight when tablets were split by patients and nurses.13 Hill et al. (2009) found that 3 out of 6 drugs presented up to 33% of split portions outside the specification adopted for weight variation when splitting tablets with a tablet splitter.7 More than 40% of hand broken hydrochlorothiazide tablets were out of specification for target weight in the study performed by McDevitt et al. (1998).5 Regarding weight variation, our results showed that splitting clonazepam tablets either by tablet splitter or kitchen knife resulted in statistically equal portions; however, these portions presented high weight variability (RSD>6%), ranging around ± 25% for tablets split by tablet splitter and ± 18% for tablets split by kitchen knife.

Although the split portions did not statistically differed from target weight, which is an indication of an apparent accurate and consistent dose administration, the high variability between split portions observed in all cases shows that the splitting was not precise, resulting in fluctuation between daily doses.

Clonazepam is a potent long-acting drug that requires dose adjustment according to patient response and treatment stage. Variations in daily drug doses due to uneven splitting might compromise gradual tapering and titration; however, it is unknown if these differences would predict any clinical effects.

Limitations of this study include that a best case scenario (trained operators and laboratory environment) was applied and only weight variation was evaluated. Other tests such as drug content uniformity, kinetics of dissolution and chemical quantitative analysis might be applied in further studies. Lastly, this study does not allow clinical conclusions once only tablet related evaluations were assessed.

Manufacturers should make an effort to introduce a wider range of strengths or liquid formulations in order to provide an alternative for tablet splitting, especially for critical medications. At the same time, health care professionals and patients should be aware of the problems related to tablet splitting and consider the risk-benefit balance of tablet splitting together with other alternatives to continue treatment.²⁰

limitações do estudo, podemos citar algumas delas: muitos idosos recusaram-se a participar das avaliações, houve dificuldades de transporte pelo fato da ILPI possuir um número restrito de cuidadores dificultando o acompanhamento às avaliações e ainda os idosos cansavam-se com muita facilidade, sendo necessários interromper os procedimentos por várias vezes.

Esse estudo evidencia a necessidade de medidas de intervenção nas ILPI, como treinamento auditivo e mudanças referentes ao convívio entre os idosos. Ambos auxiliariam nos processos de plasticidade neural e, conseqüentemente, melhora da qualidade de vida dessa população.

Considerações Finais

These preliminary findings indicate that splitting clonazepam tablets either by tablet splitter or kitchen knife might result in an apparent accurate splitting, in spite of the lack of precision between split portions. However, these findings can not be extrapolated to all cases. Future research is needed to evaluate the safety of tablet splitting, and also to further investigate if such variations in clonazepam daily drug doses would result in clinical outcomes. Nevertheless, whole tablets are still the safest way to ensure the dosage.

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